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ORIGINAL REPORT

Early Chemotherapy Intensification With Escalated BEACOPP in Patients With Advanced-Stage Hodgkin Lymphoma With a Positive Interim Positron Emission Tomography/Computed Tomography Scan After Two ABVD Cycles: Long-Term Results of the GITIL/FIL HD 0607 Trial

Andrea Gallamini, Corrado Tarella, Simonetta Viviani, Andrea Rossi, Caterina Patti, Antonino Mulé, Marco Picardi, Alessandra Romano, Maria Cantonetti, Giorgio La Nasa, Livio Trentin, Silvia Bolis, Davide Rapezzi, Roberta Battistini, Daniela Gottardi, Paolo Gavarotti, Paolo Corradini, Michele Cimminiello, Corrado Schiavotto, Guido Parvis, Roberta Zanotti, Guido Gini, Andrés J.M. Ferreri, Piera Viero, Maurizio Miglino, Atto Billio, Abraham Avigdor, Alberto Biggi, Federico Fallanca, Umberto Ficola, Michele Gregianin, Agostino Chiaravalloti, Giuseppe Prosperini, Fabrizio Bergesio, Stephane Chauvie, Chiara Pavoni, Alessandro Massimo Gianni, and Alessandro Rambaldi

Author affiliations and support information (if applicable) appear at the end of this article.

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Corresponding author: Alessandro Rambaldi, MD, Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Piazza OMS, 1, 24027 Bergamo, Italy; e-mail: alessandro.rambaldi@unimi.it.

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ABSTRACT

Purpose

To investigate the progression-free survival (PFS) of patients with advanced Hodgkin lymphoma (HL) after a risk-adapted treatment strategy that was based on a positive positron emission tomography scan performed after two doxorubicin, vinblastine, vincristine, and dacarbazine (ABVD) cycles (PET2).

Patients and Methods

Patients with advanced-stage (IIB to IVB) HL were consecutively enrolled. After two ABVD cycles, PET2 was performed and centrally reviewed according to the Deauville five-point scale. Patients with a positive PET2 were randomly assigned to four cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) followed by four cycles of standard BEACOPP with or without rituximab. Patients with a negative PET2 continued ABVD, and those with a large nodal mass at diagnosis (≥ 5 cm) in complete remission with a negative PET at the end of chemotherapy were randomly assigned to radiotherapy or no further treatment. The primary end point was 3-year PFS.

Results

Of 782 enrolled patients, 150 (19%) had a positive and 630 (81%) a negative PET2. The 3-year PFS of all patients was 82%. The 3-year PFS of those with a positive and negative PET2 was 60% and 87%, respectively ($P < .001$). The 3-year PFS of patients with a positive PET2 assigned to BEACOPP with or without rituximab was 63% versus 57% ($P = .53$). In 296 patients with both interim and post-ABVD–negative PET who had a large nodal mass at diagnosis, radiotherapy was randomly added after chemotherapy without a significant PFS improvement (97% *v* 93%, respectively; $P = .29$). The 3-year overall survival of all 782 patients was 97% (99% and 89% for PET2 negative and positive, respectively).

Conclusion

The PET-driven switch from ABVD to escalated BEACOPP is feasible and effective in high-risk patients with advanced-stage HL.

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INTRODUCTION

In the context of randomized clinical trials, patients with advanced-stage classic Hodgkin lymphoma (HL) treated with a standard doxorubicin, vinblastine, vincristine, and dacarbazine (ABVD) program achieved a 3- to 5-year progression-free survival (PFS) that ranged from 61% to 76%,[1-7] with a significant proportion of treatment failures as

ASSOCIATED CONTENT

Appendix
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a result of either refractory or relapsing disease.[1,3,8] The use of a more-intensive regimen, such as escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP), has shown superior disease control, with a 5-year freedom from treatment failure achieved in up to 90% of patients.[9,10] These remarkable results, however, occur at the cost of an increased hematologic toxicity, a high incidence of sterility,[11-13] and severe late complications/long-term toxicities, including a 5-year cumulative risk of myelodysplastic syndrome or acute leukemia of 2.2% compared with only 0.4% for ABVD.[14] For these reasons, avoidance of excessive toxicity in most patients with a risk-adapted strategy is a major treatment goal. ^{18}F-fluoro-deoxy-D-glucose positron emission tomography (PET) performed after one[15,16] or two[17,18] ABVD cycles has proven effective in predicting treatment outcome of advanced-stage HL. On the basis of these observations, we launched a multicenter prospective trial in 2008 aimed to reserve escalated BEACOPP, the most-effective frontline treatment currently available, for only patients who were at the highest risk of chemotherapy resistance as defined by a positive early interim PET scan.

PATIENTS AND METHODS

Study Design and Procedure

This prospective, open-label, phase II study aimed to improve the overall 3-year PFS of advanced-stage HL by switching from ABVD to escalated BEACOPP for a positive early interim PET scan. The study was conducted in accordance with International Conference on Harmonization for Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent was obtained before enrollment. The study was approved by the Italian Pharmacology Agency and by the ethics committees of each center. The study was registered with the European Clinical Trials Database and ClinicalTrials.gov.

Patients

Patients had to fulfill the following criteria: histopathologic diagnosis of classic HL, age 18 to 60 years, no previous therapy, Ann Arbor stage IIB to IVB, measurable International Prognostic Score (IPS), and signed informed consent. Patients were excluded in case of concomitant or previously treated (< 5 years) neoplasia, psychiatric disorder, impaired cardiac (ejection fraction < 50%) and renal (creatinine clearance < 60 mL/min) functions, HIV or any other active uncontrolled infection, pregnancy; and uncompensated diabetes.

Treatment Plan

After a baseline PET scan, patients were treated with two cycles of ABVD followed by an early interim PET reevaluation (PET2). Patients with PET2-positive scans were randomly assigned to receive BEACOPP as defined by the German Hodgkin Study Group (four cycles of escalated + four cycles of baseline BEACOPP) with or without the addition of intravenous rituximab 375 mg/m^2 given on the day 1 of each BEACOPP course. Patients with a negative PET2 scan continued their standard ABVD treatment of a total of six cycles. Among them, those with a large nodal mass (LNM [≥ 5 cm]) at baseline and a final negative PET restaging scan were randomly assigned to consolidation radiotherapy (RT [30 Gy]) on the site of an LNM detected at diagnosis or to no further treatment (NFT). In ABVD-treated patients, no chemotherapy dose adjustment was recommended on the basis of neutropenia. The relative dose intensity (RDI) delivered for ABVD and BEACOPP was calculated as described elsewhere.[19,20]

PET Imaging and Treatment Response Evaluation

Each patient had to be scanned in the same PET site throughout the study and to agree to a centralized PET scan review performed by an independent panel of nuclear medicine experts. Because interpretation of negative results does not usually require expert review[21,22] a central revision of PET scans was planned only for patients whose PET images after the first two ABVD cycles were defined by the local site as positive or with a minimal residual uptake. PET2 scans along with scans at diagnosis were centralized and, hence, automatically distributed to a panel of three nuclear medicine expert reviewers (A.B., F.F., U.F.) by the Web platform WIDEN (Web-Based Imaging Diagnosis by Expert Network) as previously described.[21] The interpretation key for PET2 reporting was the Deauville five-point scale (DS).[23] Positive scans had a score of 4 and 5. The panel was blinded to any clinical data, and reviewers used their own workstations to score the scans independently and remotely according to blinded independent central review criteria.[24]

Statistical Analysis

This trial was designed to suggest a benefit, in terms of 3-year PFS,[1-7] of a PET response–adapted strategy. With a Simon optimal two-stage design, an α-error of 5%, a power of 90%, and an expectation to cure of approximately 85%, a minimum of 155 patients was needed for enrollment. To assess a benefit of rituximab addition to escalated BEACOPP in patients with PET2-positive scans, with an expected rescue rate of 75% after rituximab-escalated BEACOPP and of 50% after escalated BEACOPP, an α-error of 5%, and a power of 80%, 65 patients had to be randomly assigned per arm. The results of the first interim analysis showed that 19% of patients had positive PET2 scans, so 684 patients had to be enrolled to reach the required sample size of 130 randomly assigned patients with PET2-positive scans.

Survival outcomes were analyzed by intention to treat by using the Kaplan-Meier method and log-rank test. PFS was measured from the date of registration to the date of first appearance of disease progression, relapse, or death as a result of any cause; overall survival (OS) was measured from the date of registration to the date of death as a result of any cause. Predictive factors of PET2 positivity were assessed with logistic regression, whereas factors that were predictive of PFS and OS were assessed with Cox proportional hazards regression models. All reported *P* values were two-sided, and the conventional 5% significance level was fixed. Statistical analysis was performed with SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

From June 2008 to June 2014, 783 patients were enrolled in the study from 25 Italian centers and one Israeli center. After registration, one patient was excluded because the revised histopathology was consistent with a diagnosis of composite lymphoma. Median age was 31 years (range, 14 to 60 years); 49% were men; and 36% had stage IIB, 32% stage III, and 32% stage IV HL. B symptoms were recorded in 81%. The largest diameter of systemic adenopathy was < 5 cm in 328 patients, between 5 and 7 cm in 140, between 8 and 10 cm in 159, and > 10 cm in 155 patients (Table 1). The median follow-up was 3.6 years (range, 0 to 7.9 years). Two patients died during the first two cycles of ABVD as a result of disease progression and cardiac failure. Thus, 780

Table 1. Baseline Characteristics of Patients Included in the Study According to PET2 Results

Characteristic	All Patients*	PET2 Negative	PET2 Positive	*P*
No. of patients	782	630	150	
Median age (range), years	31 (14-60)	31 (14-60)	30.5 (18-60)	.385
≥ 50	79 (10.1)	61 (26.5)	17 (11.3)	.545
Sex				.036
Male	382 (48.9)	297 (47.1)	85 (56.7)	
Female	400 (51.1)	333 (52.9)	65 (43.3)	
WHO activity index				.122
0-1	707 (90.4)	576 (91.4)	131 (87.3)	
> 1	73 (9.3)	54 (8.6)	19 (12.7)	
Ann Arbor stage				.284
II	279 (35.7)	229 (36.3)	50 (33.3)	
III	252 (32.2)	208 (33.0)	44 (29.3)	
IV	251 (32.1)	193 (30.6)	56 (37.3)	
IPS				< .001
0-1	286 (36.6)	251 (39.8)	35 (23.3)	
2-3	398 (50.9)	311 (49.4)	87 (58.0)	
> 3	98 (12.5)	68 (10.8)	28 (18.7)	
Large nodal mass, cm				< .001
< 5	328 (41.9)	277 (44.0)	49 (32.7)	
5-7	140 (17.9)	123 (19.5)	17 (11.3)	
8-10	159 (20.3)	117 (18.6)	42 (28.0)	
> 10	155 (19.8)	113 (17.9)	42 (28.0)	
B symptoms	634 (81.1)	511 (81.1)	121 (80.7)	.901

NOTE. Data are presented as No. (%) except where noted.
Abbreviations: IPS, International Prognostic Score; PET2, ^{18}F-fluoro-deoxy-D-glucose positron emission tomography performed after two doxorubicin, vinblastine, vincristine, and dacarbazine cycles.
*Two patients died before undergoing PET2 scanning.

patients underwent PET2 scanning. The entire study flow is shown in Figure 1.

Clinical Response, Dose Intensity, and Survival

After two cycles of ABVD, 413 of 780 PET2 scans underwent blinded independent central review with a mean (median) review time of 71 (48) hours. The reviewers unanimously agreed on 356 scans (86%), whereas with the remaining 57 (14%) scans, the majority of reviewers (ie, two of three) defined the final result. Of 780 patients, 150 (19%) had a positive and 630 (81%) a negative PET2 scan. Patients with PET2-positive results were more frequently male (57% *v* 47%; $P = .036$), had a higher IPS ($P < .001$), and had a larger nodal mass ($P < .001$). Most patients with PET2-positive results (149 of 150), were randomly assigned to the escalated BEACOPP program, with 76 patients allocated to receive only chemotherapy and 72 to receive the rituximab supplement. One patient was not randomly assigned and received escalated BEACOPP on the basis of medical decision. During the first four escalated BEACOPP cycles, seven patients withdrew consent and underwent alternative treatment, three patients died as a result of disease progression (n = 2) and infection (n = 1), one patient progressed, and two patients stopped treatment as a result of toxicity. After four escalated BEACOPP cycles, a PET evaluation was performed in 136 patients, and at the end of the study program, disease progression was registered in 27 of 108 PET-negative scans compared with 25 of 28 PET-positive scans (Fig 1).

Of the 630 patients with PET2-negative results, 629 continued with four additional ABVD cycles of whom 545 (86%) achieved a durable complete response (CR), 81 (13%) experienced treatment failure, and four withdrew consent. Of the 296 with an LNM at baseline and a negative final PET scan, 148 were randomly assigned to consolidation RT on the initial nodal site of disease and 148 to NFT.

The RDI in the two initial ABVD cycles was 97%, whereas the RDI for the additional four ABVD cycles in patients with PET2-negative results was 96%. For the BEACOPP-treated patients, the RDI was 85% (escalated BEACOPP, 85%; escalated BEACOPP with rituximab, 84%).

By intention-to-treat analysis, 629 of 782 patients remained in first CR, with a 3-year PFS and OS of 82% (95% CI, 79% to 84%) and 97% (95% CI, 95% to 98%), respectively (Figs 2A and 2B). For patients with PET2-positive and -negative results, the 3-year PFS rate was 60% (95% CI, 51% to 68%) and 87% (95% CI, 84% to 89%; Fig 2C), respectively, whereas the 3-year OS rate was 89% (95% CI, 82% to 93%) and 99% (95% CI, 97% to 99%; Fig 2D), respectively. The 3-year event-free survival of patients with PET2-positive and -negative results was identical to the PFS value because no secondary cancers have been reported so far, and only one late pulmonary toxicity was observed in a patient treated with ABVD.

No outcome difference was observed for patients allocated to rituximab-supplemented BEACOPP compared with BEACOPP, with a CR rate of 65% versus 63%, a 3-year PFS rate of 63% (95% CI, 50% to 74%) versus 57% (95% CI, 45% to 68%; $P = .53$), and a 3-year OS rate of 89% (95% CI, 79% to 95%) versus 90% (95% CI, 78% to 95%), respectively (Figs 3A and 3B). The outcome of BEACOPP was significantly different when patients with PET2-positive scans were analyzed according to DS score. In patients with a DS score of 4 versus 5, the 3-year PFS rate was 73% (95% CI, 62% to 81%) versus 35% (95% CI, 22% to 49%; $P < .001$), respectively,

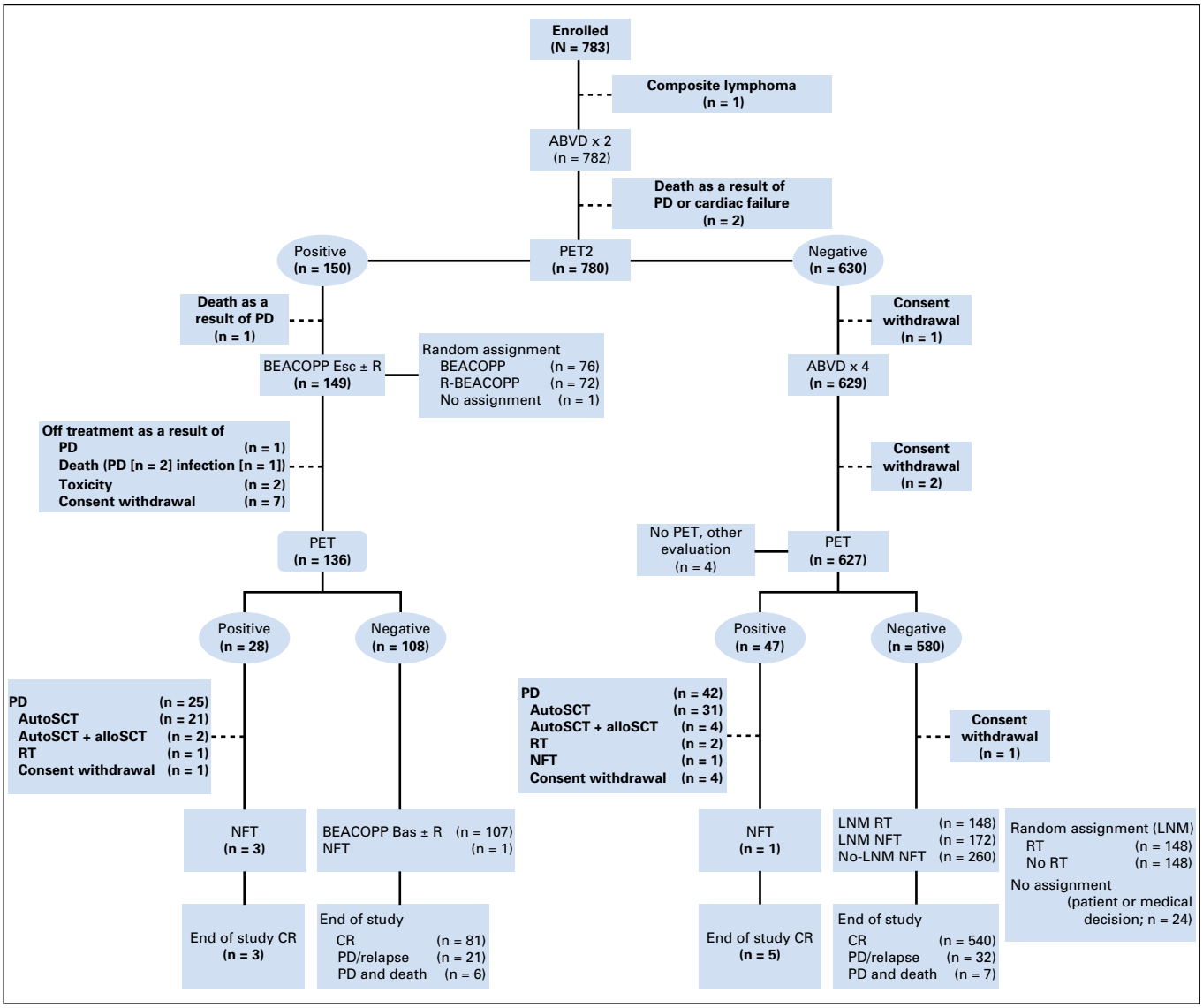

Fig 1. CONSORT diagram. ABVD, doxorubicin, vinblastine, vincristine, and dacarbazine; alloSCT, allogeneic stem-cell transplantation; autoSCT, autologous stem-cell transplantation; Bas, baseline; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CR, complete remission; Esc, escalated; LNM, large nodal mass; NFT, no further treatment; PD, progressive disease; PET2, ^{18}F-fluoro-deoxy-D-glucose positron emission tomography performed after ABVD cycles; R, rituximab; RT, radiotherapy.

and the 3-year OS rate was 92% (95% CI, 84% to 96%) versus 83% (95% CI, 67% to 92%; $P < .001$), respectively (Figs 3C and 3D).

In patients with PET-negative results in CR after six ABVD cycles, the addition of consolidation RT over an LNM detected at baseline did not translate into a significant clinical benefit compared with patients who did not undergo RT, with a 3-year PFS rate of 97% (95% CI, 92% to 99%) for RT versus 93% (95% CI, 87% to 96%) for NFT ($P = .29$), respectively, and a 3-year OS rate of 100% versus 99% (95% CI, 95% to 100%), respectively (Figs 4A and 4B). When the analysis was limited to patients with an LNM > 10 cm, the 3-year PFS rate was 94% (95% CI, 82% to 98%) for consolidation RT and 86% (95% CI, 73% to 93%) for NFT ($P = .34$). The PFS rate of the 260 patients with no LNM at baseline and not randomly assigned to RT was 92% (95% CI, 88% to 95%).

For patients randomly assigned to receive RT, this consolidation was omitted only in three of the 15 who did not have a residual mass. When the analysis was limited to those with residual mass, the relapse rate was 3% for those assigned to RT versus 6% of those who were not, with a 3-year PFS rate of 96% (95% CI, 90% to 98%) versus 93% (95% CI, 86% to 96%), respectively ($P = .39$). Overall, the 3-year relapse-free survival rate of patients with PET2-negative results was 94% (95% CI, 91% to 96%). The PET results at the end of six ABVD cycles were positive in 47 (7%) of 630 patients with PET2-negative results. After salvage treatment, an overall CR was achieved in 31 (72%) of 43 evaluable patients. A high-dose chemotherapy program was given to 35 patients who achieved a CR rate of 66%; 71% of them were alive at last follow-up.

Toxicity and Causes of Death

Toxicity was assessed on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

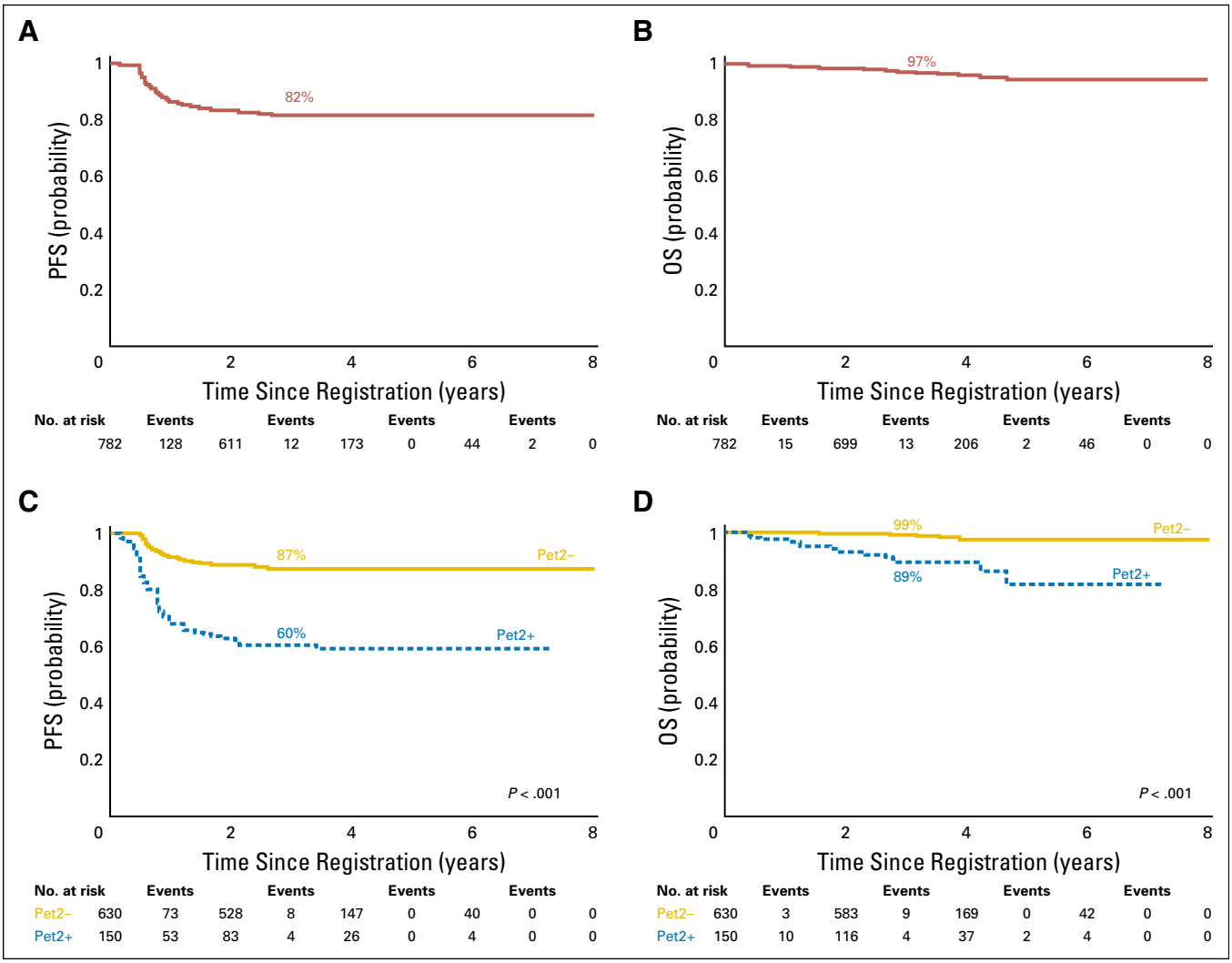

Fig 2. (A) Progression-free survival (PFS) and (B) overall survival (OS) for all patients enrolled in the study. (C) PFS and (D) OS according to positive (+) and negative (–) results for ^{18}F-fluoro-deoxy-D-glucose positron emission tomography performed after two doxorubicin, vinblastine, vincristine, and dacarbazine cycles (PET2).

During the first two ABVD cycles, grade 3 to 4 neutropenia was recorded in 323 patients (41%). Other toxicities, including GI (grade 3 nausea/vomiting), pulmonary (grade 3 infection), and metabolic (grade 3 increase of ALT and AST) were recorded in < 1% of patients. In patients who switched to BEACOPP, grade 3 to 4 hematologic toxicities were recorded in 76%. Grade 3 and 4 infections occurred in 10% of patients. In patients who continued with ABVD, a grade 3 to 4 hematologic toxicity occurred in 30% and a grade 3 pulmonary toxicity in 2% (Table 2). Overall, 30 patients (3.8%) died as a result of disease progression and cardiac failure (n = 2), resistant or progressive disease (n = 18), transplant-related toxicity (n = 5), infections (n = 4), and pulmonary fibrosis (n = 1). Between patients with PET2-positive and -negative results, 16 (11%) of 150 and 12 (2%) of 630 died, respectively.

Predictive Factors of Outcome

By univariable analysis, at diagnosis, predictive factors of a positive PET2 scan were male sex ($P = .037$), LNM > 7 cm ($P < .001$), and IPS > 1 ($P < .001$). By multivariable analysis, LNM ($P < .001$) and IPS ($P < .001$) retained their significant predictive value (Appendix Table A1, online only). By multivariable analysis, factors predictive of PFS were IPS ($P = .003$) and WHO activity index ($P = .007$), whereas the latter was the only factor that affected OS ($P = .019$; Appendix Table A2, online only).

DISCUSSION

In this study, we showed that a PET-driven switch from ABVD to escalated BEACOPP can be safely done in advanced-stage HL. With an adequate prolonged follow-up, the final results of this trial showed a 3-year PFS of 82%, three points lower than hypothesized (85%) by the study design. The interim treatment response assessment by PET imaging confirmed its high negative predictive value for treatment outcome.[17,18] The PET scan central review was feasible and allowed for timely allocation to escalated BEACOPP only in patients at the highest risk of disease resistance and recurrence. Of note, the proportion of patients with PET2-negative scans is highly comparable with that reported by other investigators.[25,26]

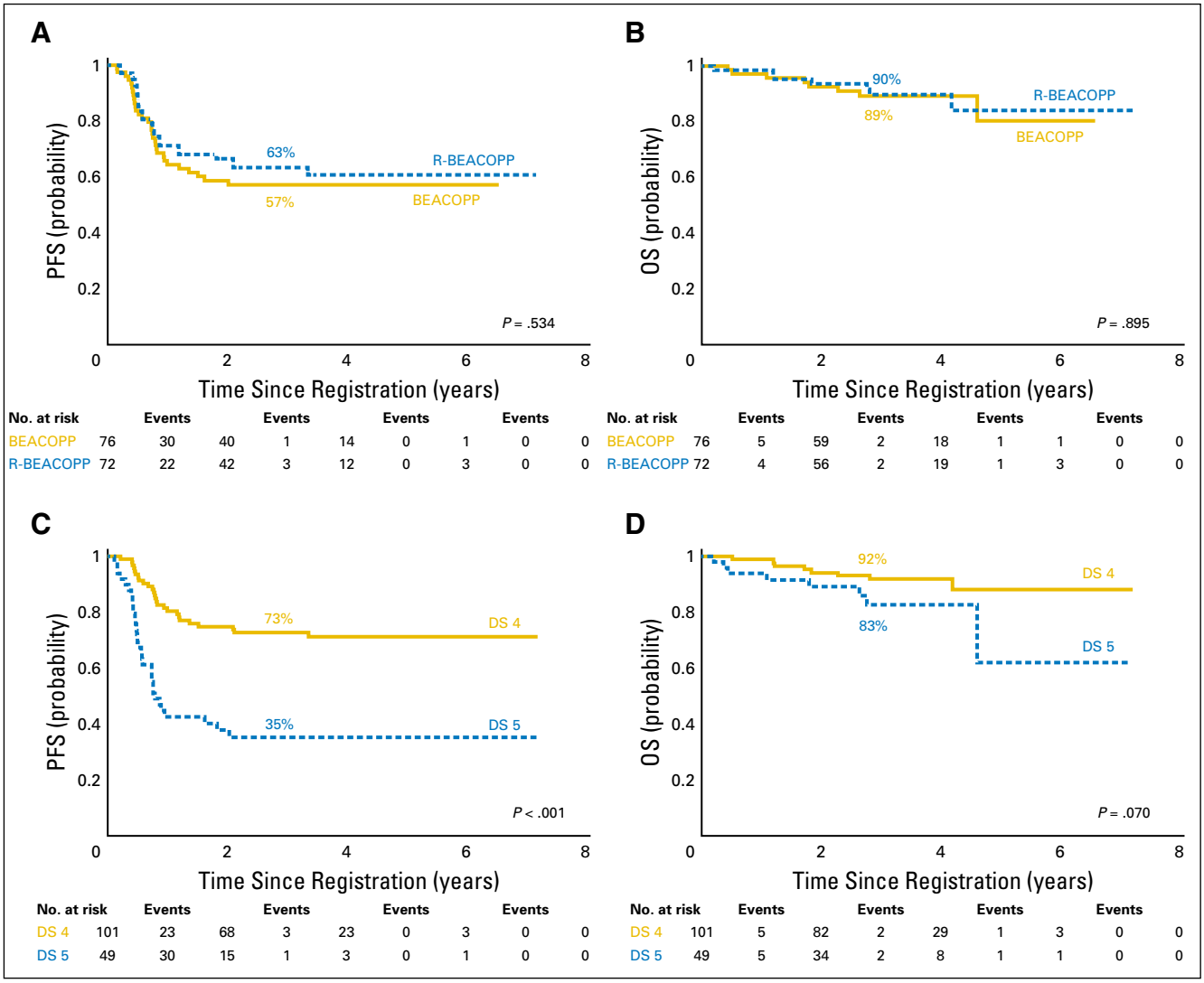

Fig 3. (A) Progression-free survival (PFS) and (B) overall survival of patients with positive results for ^{18}F-fluoro-deoxy-D-glucose positron emission tomography performed after two doxorubicin, vinblastine, vincristine, and dacarbazine cycles (PET2) randomly assigned to bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) with or without rituximab (R). (C) PFS and (D) OS of patients with PET2-positive results according to Deauville five-point scale (DS) score of 4 or 5.

As expected, escalated BEACOPP retained its robust anti-lymphoma activity, particularly in patients with a DS score of 4, who represented the majority of those with PET2-positive results. Patients with a DS score of 5 (6% of the study population), however, had a much-less-favorable response to BEACOPP. This small subset clearly deserves innovative treatment approaches.[27,28] Despite negative PET2 results, a sizeable proportion of patients (13%), which is higher than reported in previous retrospective studies,[17,18,29] experienced early or late ABVD treatment failure. This point represents a true limit of the negative predictive value of interim PET during ABVD treatment, although it was more frequently observed in patients with a higher IPS and stage IV disease. Despite treatment failure after ABVD, most of these patients were rescued by salvage high-dose chemotherapy programs. Therefore, although the clinical parameters related to disease spread and host response[30] remain unable to identify patients with poor prognosis,[31] this study confirms that an interim PET is a powerful predictor of treatment outcome.[17,18] In keeping with other prospective studies,[25,26,32] the current results suggest that a PET2-driven strategy is feasible and that escalated BEACOPP is an effective salvage treatment of patients with PET2-positive results.[25,32]

As secondary end points of this trial, we evaluated in two randomly assigned cohorts the role of rituximab added to BEACOPP in patients with PET2-positive results and the role of consolidation RT in patients with PET2-negative results and an LNM at baseline and a negative final PET scan after ABVD. Despite encouraging preliminary results on CD20 targeting with rituximab in HL[33] and in keeping with the observation of Borchmann et al,[34] no clinical benefit was gained by the combined administration of rituximab and escalated BEACOPP. In addition and similarly to what was reported by the German HD15 trial,[10] we found that in patients with PET2-negative scans, consolidation RT given at the end of ABVD in those with a negative end-of-treatment PET scan does not provide a significant advantage for

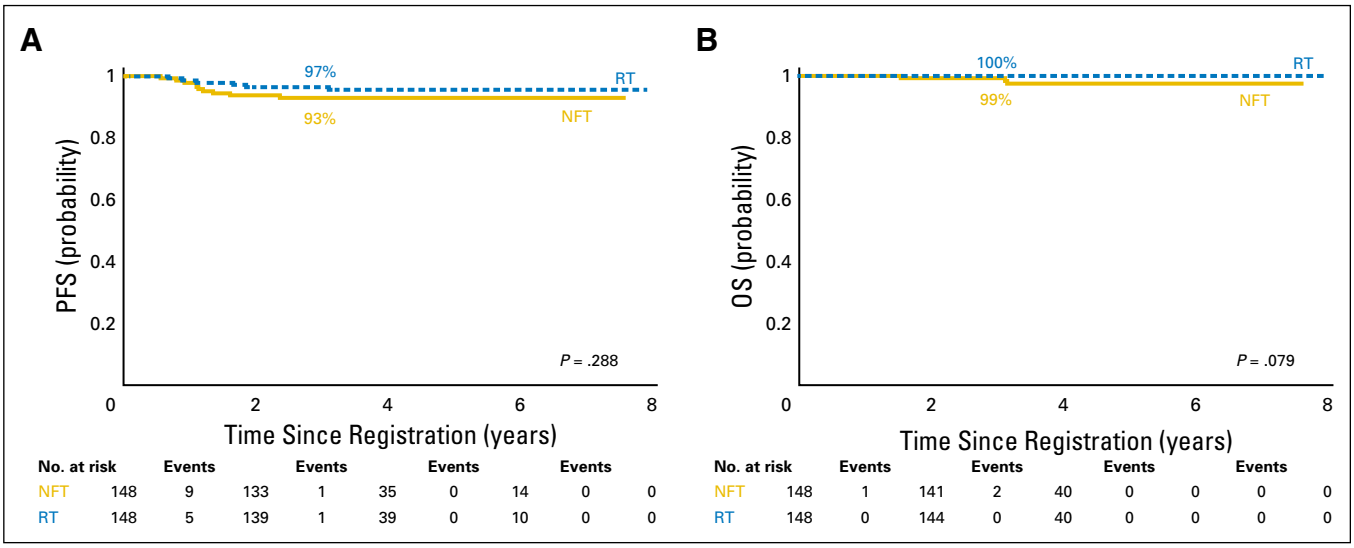

Fig 4. (A) Progression-free survival (PFS) and (B) overall survival (OS) of patients with negative results for ^{18}F-fluoro-deoxy-D-glucose positron emission tomography performed after two doxorubicin, vinblastine, vincristine, and dacarbazine cycles (PET2) randomly assigned to radiotherapy (RT) or no further treatment (NFT).

long-term disease control. This result was independent from the size of the nodal mass measured at baseline and the residual nodal enlargement measured at the end of ABVD. Although consolidation RT on LNM was originally included by the Milan group in the standard ABVD program, this observation underlines the discriminative role of PET after ABVD to guide consolidation RT in patients with an LNM. Although, the sample size of this study was not calculated on the RT substudy and caution is needed for a wise interpretation, this result is clinically relevant when considering the long-term safety issues in the treatment strategy for patients with HL.[35,36] The cost-effectiveness of repeat PET imaging at the end of six ABVD cycles is suggested by the CR rate achieved by the salvage treatments on the basis of PET results, even if disease control of a frontline treatment on the basis of escalated BEACOPP remains superior (PFS rate > 90%) without the need of PET-guided treatment.[34,37] Another secondary study end point was the toxicity of the overall treatment strategy, which is in keeping with that already described for ABVD[3] and escalated BEACOPP.[9,10] In patients who were switched to BEACOPP, hematologic toxicity remained significantly higher than with ABVD, even though the treatment-related mortality was low and mostly a result of second or third salvage treatments.

In conclusion, similar to UK Response Adapted Therapy in Advanced Hodgkin Lymphoma[38] and the American S0816[25] trials that share the same trial backbone, the GITIL/FIL HD 0607 trial demonstrates that a PET response–adapted treatment is a feasible, safe, and effective therapeutic strategy in advanced-stage HL. Moreover, consolidation RT on an LNM recorded at baseline could be safely omitted in patients with both interim and end-of-treatment negative PET scans.

Table 2. Toxicities Assessed by National Cancer Institute Common Terminology Criteria for Adverse Events (Version 3.0)

	Highest Grade, No. (%)					
	Pre-PET2 (n = 782)		PET2 Negative (n = 630)		PET2 Positive (n = 150)	
Adverse Event	1-2	3-4	1-2	3-4	1-2	3-4
Blood/bone marrow	105 (13)	323 (41)	109 (17)	189 (30)	4 (3)	114 (76)
GI	48 (6)	6 (1)	38 (6)	6 (1)	17 (11)	0 (0)
Infection	17 (2)	5 (1)	33 (5)	5 (1)	12 (8)	16 (10)
Pulmonary/upper respiratory	6 (1)	2 (< 1)	30 (5)	11 (2)	9 (6)	1 (1)
Constitutional symptoms	4 (1)	0 (0)	18 (3)	1 (< 1)	15 (10)	2 (1)
Vascular	8 (1)	0 (0)	14 (2)	2 (< 1)	10 (7)	2 (1)
Neurology	5 (1)	0 (0)	11 (2)	1 (< 1)	13 (9)	2 (1)
Pain	6 (1)	0 (0)	8 (1)	0 (0)	6 (4)	1 (1)
Dermatology/skin	3 (< 1)	0 (0)	11 (2)	0 (0)	5 (3)	1 (1)
Metabolic/laboratory	5 (1)	6 (1)	1 (< 1)	0 (0)	4 (3)	0 (0)
Cardiac arrhythmia/cardiac general	3 (< 1)	1 (< 1)	4 (1)	2 (< 1)	4 (3)	3 (2)
Musculoskeletal/soft tissue	2 (< 1)	0 (0)	2 (< 1)	3 (< 1)	2 (1)	3 (2)
Allergy/immunology	4 (1)	1 (< 1)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatobiliary/pancreas	0 (0)	3 (< 1)	1 (< 1)	0 (0)	0 (0)	0 (0)
Coagulation	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)

Abbreviation: PET2, ^{18}F-Fluoro-deoxy-D-glucose positron emission tomography performed after two doxorubicin, vinblastine, vincristine, and dacarbazine cycles.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Andrea Gallamini, Corrado Tarella, Paolo Corradini, Alessandro Massimo Gianni, Alessandro Rambaldi
Provision of study materials or patients: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: Andrea Gallamini, Corrado Tarella, Simonetta Viviani, Stephane Chauvie, Chiara Pavoni, Alessandro Massimo Gianni, Alessandro Rambaldi
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Affiliations

Andrea Gallamini, Centre Antoine Lacassagne, Nice, France; **Corrado Tarella**, Istituto Europeo di Oncologia; **Daniela Gottardi**, Ospedale Mauriziano Umberto I di Torino; **Paolo Gavarotti**, Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino, Turin; **Simonetta Viviani** and **Paolo Corradini**, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Nazionale dei Tumori; **Paolo Corradini**, **Alessandro Massimo Gianni**, and **Alessandro Rambaldi**, Università degli Studi di Milano; **Andrés J.M. Ferreri** and **Federico Fallanca**, Istituto di Ricovero e Cura a Carattere Scientifico Ospedale San Raffaele; **Giuseppe Prosperini**, Istituto di Ricovero e Cura a Carattere Scientifico-Istituto di Ricerche Farmacologiche Mario Negri, Milan; **Andrea Rossi**, **Chiara Pavoni**, and **Alessandro Rambaldi**, Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Bergamo; **Caterina Patti** and **Antonino Mulé**, Azienda Villa Sofia-Cervello; **Umberto Ficola**, La Maddalena, Palermo; **Marco Picardi**, Università Federico II, Naples; **Alessandra Romano**, Ospedale Ferrarotto, Catania; **Maria Cantonetti**, Policlinico Tor Vergata; **Roberta Battistini**, Ospedale San Camillo; **Agostino Chiaravalloti**, Università Tor Vergata, Rome; **Giorgio La Nasa**, Ospedale Roberto Binaghi di Cagliari, Cagliari; **Livio Trentin**, Università di Padova, Padua; **Silvia Bolis**, Ospedale San Gerardo, Monza; **Davide Rapezzi**, **Alberto Biggi**, **Fabrizio Bergesio**, and **Stephane Chauvie**, Azienda Ospedaliera Santa Croce e Carle, Cuneo; **Michele Cimminiello**, Ospedale San Carlo, Potenza; **Corrado Schiavotto**, Presidio Ospedaliero San Bortolo, Vicenza; **Guido Parvis**, Azienda Ospedaliera San Luigi, Orbassano; **Roberta Zanotti**, Azienda Ospedaliera Universitaria Integrata, Verona; **Guido Gini**, Nuovo Ospedale Torrette, Ancona; **Piera Viero**, Ospedale dell'Angelo, Mestre; **Maurizio Miglino**, Azienda Ospedaliera Universitaria San Martino, Genoa; **Atto Billio**, Ospedale Centrale di Bolzano, Bolzano; **Michele Gregianin**, Ospedale San Giacomo, Castelfranco Veneto, Italy; and **Abraham Avigdor**, Chaim Sheba Medical Center, Tel HaShomer, Israel.

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Andrea Gallamini
Honoraria: Takeda Pharmaceuticals
Consulting or Advisory Role: Takeda Pharmaceuticals

Corrado Tarella
Travel, Accommodations, Expenses: Amgen, Celgene, Roche

Simonetta Viviani
Honoraria: Takeda Pharmaceuticals
Consulting or Advisory Role: Takeda Pharmaceuticals, Italfarmaco
Speakers' Bureau: Takeda Pharmaceuticals
Research Funding: Takeda Pharmaceuticals
Travel, Accommodations, Expenses: Takeda Pharmaceuticals, Celgene

Andrea Rossi
Travel, Accommodations, Expenses: Roche, Takeda Pharmaceuticals

Caterina Patti
No relationship to disclose

Antonino Mulé
No relationship to disclose

Marco Picardi
No relationship to disclose

Alessandra Romano
Travel, Accommodations, Expenses: Takeda Pharmaceuticals

Maria Cantonetti
Consulting or Advisory Role: Roche
Speakers' Bureau: Takeda Pharmaceuticals, Roche
Research Funding: Roche, Novartis, Takeda Pharmaceuticals
Travel, Accommodations, Expenses: Takeda Pharmaceuticals, Roche, Mundipharma, Gilead Sciences

Giorgio La Nasa
No relationship to disclose

Livio Trentin
Research Funding: Gilead Sciences

Silvia Bolis
No relationship to disclose

Davide Rapezzi
Research Funding: Takeda (Inst)
Travel, Accommodations, Expenses: Novartis, Alexion Pharmaceuticals, Incyte, Genzyme, Jazz Pharmaceuticals

Roberta Battistini
No relationship to disclose

Daniela Gottardi
No relationship to disclose

Paolo Gavarotti
No relationship to disclose

Paolo Corradini
Honoraria: Celgene, Janssen Pharmaceuticals, Novartis, Takeda Pharmaceuticals, Gilead Sciences, Roche, Sanofi
Travel, Accommodations, Expenses: Novartis, Celgene, Roche, Takeda Pharmaceuticals, Gilead Sciences

Michele Cimminiello
No relationship to disclose

Corrado Schiavotto
No relationship to disclose

Guido Parvis
No relationship to disclose

Roberta Zanotti
Consulting or Advisory Role: Deciphera Pharmaceuticals

Guido Gini
Honoraria: Pfizer, Servier, TEVA Pharmaceuticals Industries, Takeda Pharmaceuticals
Consulting or Advisory Role: TEVA Pharmaceuticals Industries, Pfizer, Takeda Pharmaceuticals
Travel, Accommodations, Expenses: Roche, TEVA Pharmaceuticals Industries, Pfizer, Gilead Sciences, Vifor Pharma, Takeda Pharmaceuticals

Andrés J.M. Ferreri
No relationship to disclose

Piera Viero
No relationship to disclose

Maurizio Miglino
No relationship to disclose

Atto Billio
No relationship to disclose

Abraham Avigdor
No relationship to disclose

Alberto Biggi
No relationship to disclose

Federico Fallanca
No relationship to disclose

Umberto Ficola
No relationship to disclose

Michele Gregianin
No relationship to disclose

Agostino Chiaravalloti
No relationship to disclose

Giuseppe Prosperini
No relationship to disclose

Fabrizio Bergesio
No relationship to disclose

Stephane Chauvie
Stock or Other Ownership: Dixit
Travel, Accommodations, Expenses: Sirtex Medical, BTG International, GE Healthcare, Philips Medical System

Chiara Pavoni
No relationship to disclose

Alessandro Massimo Gianni
No relationship to disclose

Alessandro Rambaldi
Consulting or Advisory Role: Novartis, Roche, Genentech, Amgen, Italfarmaco
Travel, Accommodations, Expenses: Novartis, Celgene, Amgen, Sanofi

Appendix

Table A1. Univariable and Multivariable Analysis for PET2 Positivity

	Univariable		Multivariable	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age, years				
< 50	1.00			
≥ 50	1.19 (0.67 to 2.11)	.545		
Sex				
Female	1.00			
Male	1.47 (1.02 to 2.10)	.037		
WHO activity index				
0-1	1.00		1.00	
> 1	1.55 (0.89 to 2.70)	.124	1.23 (0.69 to 2.19)	.480
Stage				
II-III	1.00			
IV	1.35 (0.93 to 1.96)	.114		
IPS				
0-1	1.00		1.00	
> 1	2.18 (1.44 to 3.28)	< .001	2.15 (1.42 to 3.28)	< .001
Bulky disease, cm				
< 7	1.00		1.00	
≥ 7	2.21 (1.54 to 3.18)	< .001	2.22 (1.54 to 3.20)	< .001
B symptoms				
No	1.00		1.00	
Yes	0.97 (0.62 to 1.53)	.900	0.81 (0.51 to 1.29)	.372

Abbreviations: IPS, International Prognostic Score; OR, odds ratio; PET2, ^{18}F-Fluoro-deoxy-D-glucose positron emission tomography performed after two doxorubicin, vinblastine, vincristine, and dacarbazine cycles.

Table A2. Multivariable Analysis for Progression-Free Survival and Overall Survival in All Patients

	Progression-Free Survival		Overall Survival	
	HR (95% CI)	*P*	HR (95% CI)	*P*
WHO activity index				
0-1	1.00		1.00	
> 1	1.87 (1.19 to 2.93)	.007	2.70 (1.17 to 6.19)	.019
IPS				
0-1	1.00		1.00	
> 1	1.83 (1.23 to 2.73)	.003	2.26 (0.85 to 6.01)	.101
Bulky disease, cm				
< 7	1.00		1.00	
≥ 7	1.29 (0.92 to 1.80)	.143	1.43 (0.69 to 2.95)	.334
B symptoms				
No	1.00		1.00	
Yes	1.26 (0.79 to 2.01)	.330	5.76 (0.78 to 42.48)	.086

Abbreviations: HR, hazard ratio; IPS, International Prognostic Score.